New Formulation for Derivatives of Torsion Angles and Improper Torsion Angles in Molecular Mechanics: Elimination of Singularities

ARNAUD BLONDEL and MARTIN KARPLUS

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138 and Laboratoire de Chime Biophysique, Institut Le Bel, Université Louis Pasteur, 67000 Strasbourg, France

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ABSTRACT

A new set of formulae is developed for the derivatives of torsion angle energy terms and is introduced into the program CHARMM. These formulae, which are based on derivatives of the torsion angle itself, avoid the singularities introduced by use of the derivatives of the torsion angle cosine. The potential energy can include any differentiable function of the torsion angle and there is no need for a special treatment for cases where planar conformations are not extrema. The resulting code is simpler than the original version and yields correct derivatives in all practical situations. Because the minimum of the torsion energy can be at any angle, the functionality of the existing energy routines is generalized.

Introduction

An essential element of any molecular mechanics and dynamics program is the potential energy function. For most applications, derivatives of the potential function with respect to the atomic positions are required. Ordinary molecular dynamics algorithms and certain energy minimizers (e.g., steepest descent, conjugate gradient) make use of the first derivatives of the potential energy function, while special dynamics methods (e.g., Langevin/implicit–Euler),[1] more sophisticated minimizers (e.g., the Newton–Raphson method), and normal mode calculations require second derivatives. One of the important aspects of the potential functions is that the required derivatives can be calculated analytically. Since the potential energy is usually a sum of individual energy terms, the derivatives of each term can be obtained separately. For the local contributions, the derivatives

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of the bond length and bond angle terms can be evaluated in a straightforward way. However, certain complications can arise in the evaluation of the derivatives of the energy with respect to the torsion angle and improper torsion angle terms. These terms were introduced originally to explain thermodynamics data[2] and because it was not possible to model accurately the rotation barriers around bonds with only nonbonded interactions (i.e., van der Waals and electrostatic terms), while preserving at the same time the intermolecular energies that arise from the van der Waals and electrostatic terms alone.[3]

In the conventional evaluation of the torsional derivatives, the chain rule based on the cosine of the torsion angle was used (CFF,[4] ECEPP,[5] MM2,[6] or CHARMM[7]). The evaluation of the energy derivatives by use of the cosine of the angle is straightforward because the cosine is a normalized dot product. The derivatives $\partial \cos \varphi/\partial r$ and $\partial^2 \cos \varphi/\partial r^2$ are described by Niketić and Rasmussen,[8] for example, and were used in the early work on molecular mechanics force fields by Warshel and Lifson.[3] However, the approach has the drawback that the derivative $(\partial \cos \varphi/\partial r)$ is zero when $\sin \varphi$ is equal to zero. This occurs when the four atoms determining the torsion angle are in the same plane. If $\varphi = 0$ or π are not extrema of the energy function associated with the torsion, the derivatives $\partial E/\partial r$ and $\partial^2 E/\partial r^2$ are undetermined for these angles. To avoid this problem, the functional forms of the torsional energy term have been limited to $\sum_{n=0}^{N} a_n \cos(n\varphi)$ with no phase shift relative to $\varphi = 0$ (e.g., refs. 4, 6, 7–9). However, the improper torsion terms cannot be limited to such forms because they are used to maintain nonplanar equilibrium positions (e.g., the pyramidal conformation of certain sp^3 atoms). In these cases, the derivative of the potential energy has a singularity for $\sin \varphi = 0$. To avoid division by zero, a series of tests branching to approximate forms of the derivatives was introduced in the neighborhood of $\sin \varphi = 0$. Such testing was necessary even in the case of a planar equilibrium geometry to avoid a division by $\sin \varphi$; i.e., the ratio $\varphi/\sin \varphi$ was replaced by $(1 + \varphi^2/6)$, as in ref. 7. The present article presents a new approach to the singularity problem that eliminates the need for tests or the use of special functions.

The singularity that arises from the situation where at least three consecutive atoms are in the same line cannot be avoided. It has a geometrical basis because the angle φ is not defined. However, this situation is improbable because strong angle energy terms generally force the atoms to remain nonlinear. On the contrary, the singularities of the derivatives encountered at $\sin \varphi = 0$ (i.e., when the four atoms are in the same plane, a situation which is more probable) can be avoided because they have no geometrical basis in three-dimensional space. One possibility, which we describe here, is to directly calculate the derivatives with respect to φ instead of $\cos \varphi$. In previous implementations, $\partial \cos \varphi/\partial r$ and $\partial^2 \cos \varphi/\partial r^2$ were introduced because the calculation of the derivatives, $\partial \varphi/\partial r$ and $\partial^2 \varphi/\partial r^2$, is not straightforward since φ is a transcendental function of the positions; it is the arccos of a rational function. However, the first and second derivatives of φ are not transcendental functions of the positions, as is evident from the fact that φ can be written as $\varphi = -i \cdot (\ln(\cos \varphi + i \cdot \sin \varphi))$ and $\partial \ln(x)/\partial x = 1/x$.

In this article we derive expressions for the first and second derivatives of φ that are useful for calculations and test them numerically to show that accurate results are obtained. The resulting formulae have no singularities at $\sin \varphi = 0$ and can be used for any functional form of the torsional angle φ. In particular, the torsional energy is no longer limited to the form $\sum_n a_n \cos(n\varphi)$; i.e., a phase shift of the form $\sum_n a_n \cos(n \cdot (\varphi - \varphi_{0n}))$ can be used. Also, the formulation removes the need for special tests. The elimination of such tests is of importance for vector or parallel machines because it allows more efficient optimization of the algorithms. Details of the implementation in the CHARMM program[7] are described; i.e., the formulae used to calculate energy terms and their derivatives are given. A corresponding implementation in other molecular mechanics programs should be straightforward. For the first derivatives, $(\partial \varphi/\partial r)$, similar formulae were presented independently by van Schaik et al.,[10] but no derivation was given.

Method

GENERAL NOTATION

We used a common notation scheme to define the torsion angle (see Fig. 1). The formulae for the derivatives are presented in a vector or tensor form for conciseness and clarity. Since all quanti-

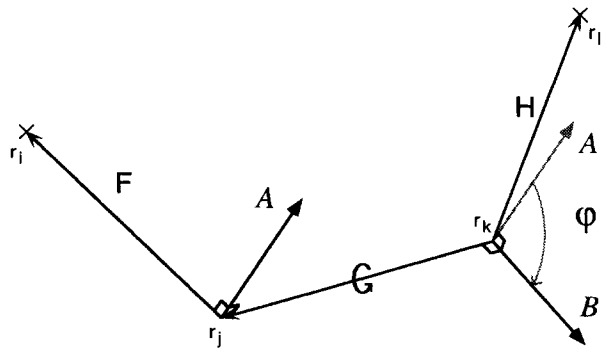

FIGURE 1. Schematic view of the vectors and angles used in the torsion angle determination [see text eqs. (1)–(4)]. Different fonts are used for (F, H), (A, B), and (r_i–r_l) to point out the different layers of intermediate vectors in eqs. (1)–(4). The vector *G* is labeled by the rotation arrow. The vector *A* (originally in black) is redrawn in grey with the same origin as vector *B* to indicate the positive orientation of φ.

ties entering the formulae are vectors or tensors, no specific vector or tensor notation is used. The symbol (A, B) is used for vector concatenation $(((x, y, z),(x', y', z')) = (x, y, z, x', y', z'))$. A dot $(\cdot)$ indicates the scalar product in any dimension. The symbol $\wedge$ is used for the vector product and $A \wedge B \cdot C = \det([ABC])$. The symbol $\otimes$ is used for the tensor product ($A \otimes B = [A_i \cdot B_j]$) and ${}^TA$ indicates the transpose of A. The symbol $\partial A/\partial V$ has to be understood as the tensor $[\partial A_j/\partial V_i]$. Indices to the vectors are given to specify to which differential they correspond only where some confusion could arise.

The positions of the atoms i, j, k, and l which define φ are given by the vectors r_i, r_j, r_k and r_l (see Fig. 1). A first set of intermediate vectors is defined by

$$F = r_i - r_j, \quad G = r_j - r_k, \quad \text{and} \quad H = r_l - r_k. \tag{1}$$

A second set of intermediate vectors is defined by

$$A = F \wedge G \quad \text{and} \quad B = H \wedge G. \tag{2}$$

The angle φ of interest can be defined by the angle between A and B in terms of the identities

$$\cos\varphi = \frac{A \cdot B}{|A||B|} \tag{3}$$

$$\sin\varphi = \frac{B \wedge A \cdot G}{|A||B||G|}. \tag{4}$$

From these definitions, the interchanges $i \leftrightarrow l$ and $j \leftrightarrow k$ give the "symmetries" $F \leftrightarrow H$, $G \leftrightarrow -G$, $A \leftrightarrow -B$, and $\varphi \leftrightarrow \varphi$, which are used to derive certain symmetry related formulae.

FIRST DERIVATIVES

The chain rule identities for the derivatives with respect to $\cos\varphi$ and φ are

$$\frac{\partial E}{\partial r} = \frac{\partial E}{\partial \cos\varphi} \cdot \frac{\partial \cos\varphi}{\partial r} \tag{5}$$

$$\frac{\partial E}{\partial r} = \frac{\partial E}{\partial \varphi} \cdot \frac{\partial \varphi}{\partial r}. \tag{6}$$

Here r stands for (r_i, r_j, r_k, r_l) so that these identities are to be understood as involving vectors with 12 elements. We calculate the derivatives of φ by using those of $\cos\varphi$.

For $\partial\varphi/\partial r$, we can write

$$\frac{\partial \varphi}{\partial r} = \frac{\partial \varphi}{\partial \cos\varphi} \cdot \frac{\partial \cos\varphi}{\partial r}. \tag{7}$$

Since

$$\frac{\partial \varphi}{\partial \cos\varphi} = \frac{-1}{\sin\varphi}, \tag{8}$$

we have

$$\frac{\partial \varphi}{\partial r} = \frac{-1}{\sin\varphi} \cdot \frac{\partial \cos\varphi}{\partial r}. \tag{9}$$

To evaluate $\partial\varphi/\partial r$ from eq. (9), we use the definition of $\cos\varphi$ and the chain rule for the vectors (A, B) and (F, G, H), which are 6- and 9-dimensional, respectively; i.e., the procedure used in the calculations is summarized in the following schematic equation:

$$\frac{\partial \varphi}{\partial r} = \frac{-1}{\sin\varphi} \cdot \frac{\partial \cos\varphi}{\partial (A, B)} \cdot \frac{\partial (A, B)}{\partial (F, G, H)} \cdot \frac{\partial (F, G, H)}{\partial r}. \tag{10}$$

From eq. (3)

$$\frac{\partial \cos\varphi}{\partial A} = \frac{B}{|A||B|} + \frac{A \cdot B}{|B|} \cdot \frac{\partial (1/|A|)}{\partial A}. \tag{11}$$

Introducing the identity

$$\frac{\partial |A|}{\partial A} = \frac{A}{|A|}, \tag{12}$$

we find

$$\frac{\partial \cos\varphi}{\partial A} = \frac{1}{|A|^3|B|}(A^2B - (A\cdot B)A). \quad (13)$$

From the double vector product formula,[11] we have the identity

$$A \wedge (B \wedge A) = A^2B - (A\cdot B)A. \quad (14)$$

Introducing eq. (14) into (13) and comparing with eq. (4) using the fact that G is perpendicular to both A and B, we obtain

$$\frac{\partial \cos\varphi}{\partial A} = \frac{1}{A^2|G|}\sin\varphi A \wedge G. \quad (15)$$

Replacing r with A in eq. (9) and substituting for $\partial\cos\varphi/\partial A$ in eq. (15), we find

$$\frac{\partial\varphi}{\partial A} = \frac{1}{A^2|G|}G \wedge A. \quad (16)$$

The step from eq. (15) to (16) involves $\sin\varphi/\sin\varphi$, thus eq. (16) is true for all φ with $\sin\varphi \neq 0$. Equation (16) is independent of H and B and thus of the value of φ. This shows that the validity of eq. (16) extends to the case $\sin\varphi = 0$. A standard continuity argument based on the ratio limit for $\sin\varphi/\sin\varphi$ going to 1 as φ tends to 0 or π, can also be used to show this.

By symmetry, we have the corresponding expression

$$\frac{\partial\varphi}{\partial B} = \frac{1}{B^2|G|}B \wedge G. \quad (17)$$

The next step is to determine the derivatives with respect to the vectors F, G, H by applying the chain rule. To calculate $\partial A/\partial F$, we use eq. (2) and find

$$\frac{\partial A}{\partial F} = \frac{\partial(F \wedge G)}{\partial F} = \mathbb{I} \wedge G. \quad (18)$$

Here $\mathbb{I}$ is the identity matrix and $\mathbb{I} \wedge G$ is defined such that $\mathbb{I} \wedge G \cdot V = V \wedge G$, where V is an arbitrary vector. The application of the chain rule using eqs. (16) and (18) gives $\partial\varphi/\partial F$ as

$$\frac{\partial\varphi}{\partial F} = \frac{^T\partial\varphi}{\partial A}\cdot\frac{\partial A}{\partial F} = \frac{1}{A^2|G|}{}^T(G \wedge A)\cdot\mathbb{I} \wedge G. \quad (19)$$

We use the transpose sign on $\partial\varphi/\partial A$ to emphasize the importance of the order of the terms in the chain rule because $\partial A/\partial F$ is antisymmetric. The evaluation of eq. (19), using the definition of $\mathbb{I} \wedge G$, yields

$$\frac{\partial\varphi}{\partial F} = -\frac{1}{A^2|G|}(G \wedge A) \wedge G. \quad (20)$$

The minus sign arises from the antisymmetry of eq. (18). With eq. (14) and the identity $(A\cdot G) = 0$, this reduces to

$$\frac{\partial\varphi}{\partial F} = -\frac{|G|}{A^2}A. \quad (21)$$

By symmetry, we have

$$\frac{\partial\varphi}{\partial H} = \frac{|G|}{B^2}B. \quad (22)$$

Using the chain rule, the equivalent of eq. (18) to obtain $\partial A/\partial G = F \wedge \mathbb{I}$ and $\partial B/\partial G = H \wedge \mathbb{I}$ and their antisymmetry, we find that

$$\frac{\partial\varphi}{\partial G} = \frac{\partial\varphi}{\partial A}\cdot\frac{\partial A}{\partial G} + \frac{\partial\varphi}{\partial B}\cdot\frac{\partial B}{\partial G} = \frac{1}{A^2|G|}(G \wedge A) \wedge F - \frac{1}{B^2|G|}(G \wedge B) \wedge H. \quad (23)$$

We replace A and B by eq. (2) and use eq. (14) to obtain

$$\frac{\partial\varphi}{\partial G} = \frac{(G^2F - (F\cdot G)G) \wedge F}{A^2|G|} - \frac{(G^2H - (H\cdot G)G) \wedge H}{B^2|G|}. \quad (24)$$

Using $F \wedge F = 0$, $H \wedge H = 0$ and eq. (2), we obtain

$$\frac{\partial\varphi}{\partial G} = \frac{(F\cdot G)}{A^2|G|}A - \frac{(H\cdot G)}{B^2|G|}B. \quad (25)$$

The last step in the application of the chain rule [Eq. (10)], requires evaluation of $\partial(F, G, H)/\partial r$. This step is usually used to distribute the derivatives in the force array of a molecular mechanics program. The nonzero terms are seen from eq. (1) to be

$$\frac{\partial F}{\partial r_i} = \mathbb{I}, \quad \frac{\partial F}{\partial r_j} = -\mathbb{I}, \quad \frac{\partial G}{\partial r_j} = \mathbb{I}, \quad \frac{\partial G}{\partial r_k} = -\mathbb{I}, \quad \frac{\partial H}{\partial r_k} = -\mathbb{I}, \text{ and } \frac{\partial H}{\partial r_l} = \mathbb{I}. \quad (26)$$

Combining the above results as in eq. (10) to obtain the derivatives $\partial\varphi/\partial r$, we have finally

$$\frac{\partial\varphi}{\partial r_i} = -\frac{|G|}{A^2}A \tag{27i}$$

$$\frac{\partial\varphi}{\partial r_j} = \frac{|G|}{A^2}A + \frac{(F\cdot G)}{A^2|G|}A - \frac{(H\cdot G)}{B^2|G|}B \tag{27j}$$

$$\frac{\partial\varphi}{\partial r_k} = \frac{(H\cdot G)}{B^2|G|}B - \frac{(F\cdot G)}{A^2|G|}A - \frac{|G|}{B^2}B \tag{27k}$$

$$\frac{\partial\varphi}{\partial r_l} = \frac{|G|}{B^2}B. \tag{27l}$$

With Eqs. (27), the energy derivative in eq. (6) can be evaluated in a straightforward manner.

SECOND DERIVATIVES

The application of the chain rule to eq. (6) provides the general framework for the second derivatives calculation. We have

$$\frac{\partial^2 E}{\partial r^2} = \frac{\partial^2 E}{\partial\varphi^2}\cdot\frac{\partial\varphi}{\partial r}\otimes\frac{\partial\varphi}{\partial r} + \frac{\partial E}{\partial\varphi}\cdot\frac{\partial^2\varphi}{\partial r^2}. \tag{28}$$

Since $\partial\varphi/\partial r$ is known [eq. (27)] and $\partial^2 E/\partial\varphi^2$ and $\partial E/\partial\varphi$ are known from the choice of the energy function, we only have to determine $\partial^2\varphi/\partial r^2$. The chain rule applied to the derivatives of φ with respect to (F, G, H) yields the schematic equation

$$\frac{\partial^2\varphi}{\partial r^2} = \frac{\partial^2\varphi}{\partial(F,G,H)^2}\cdot\frac{\partial(F,G,H)}{\partial r}\otimes\frac{\partial(F,G,H)}{\partial r} + \frac{\partial\varphi}{\partial(F,G,H)}\cdot\frac{\partial^2(F,G,H)}{\partial r^2}. \tag{29}$$

The second term on the right of eq. (29) is zero since (F, G, H) are polynomials of degree one in r. The tensorial part of the first term is obtained from eq. (26). This leaves the term $\partial^2\varphi/\partial(F,G,H)^2$ to be evaluated. We first calculate $\partial^2\varphi/\partial F^2$ as $\partial(\partial\varphi/\partial F)/\partial F$. Using eqs. (21) and (18), we have

$$\frac{\partial^2\varphi}{\partial F^2} = 2\frac{|G|}{A^4}A\otimes{}^{T}A\cdot\mathbb{I}\wedge G - \frac{|G|}{A^2}\mathbb{I}\wedge G = 2\frac{|G|}{A^4}A\otimes G\wedge A - \frac{|G|}{A^2}\mathbb{I}\wedge G. \tag{30}$$

We now introduce a symmetrization lemma:

$$A^2\cdot\mathbb{I}\wedge G + G\wedge A\otimes A - A\otimes G\wedge A = 0, \tag{31}$$

which can be shown by explicit calculation. It also follows form the fact that application of any of the three vectors $(A, G, G\wedge A)$ to the operator defined by the left-hand side of eq. (31) yields zero. These vectors define a complete set if none of them is zero; if any one of them is zero, the lemma is trivial with eq. (2).

From eqs. (30) and (31) we derive the symmetric form of $\partial^2\varphi/\partial F^2$,

$$\frac{\partial^2\varphi}{\partial F^2} = \frac{|G|}{A^4}(A\otimes G\wedge A + G\wedge A\otimes A), \tag{32}$$

and by symmetry the corresponding expression

$$\frac{\partial^2\varphi}{\partial H^2} = \frac{-|G|}{B^4}(B\otimes G\wedge B + G\wedge B\otimes B). \tag{33}$$

The cross terms are $\partial^2\varphi/\partial F\cdot\partial G$, $\partial^2\varphi/\partial F\cdot\partial H$, and $\partial^2\varphi/\partial G\cdot\partial H$. We calculate $\partial^2\varphi/\partial F\cdot\partial G$ as $\partial(\partial\varphi/\partial G)/\partial F$. As a check we have made the derivations in the other order (not shown). The derivative of eq. (25) with respect to F is

$$\frac{\partial^2\varphi}{\partial F\cdot\partial G} = \frac{\partial}{\partial F}\left(\frac{F\cdot G}{|G|A^2}A_G - \frac{H\cdot G}{|G|B^2}B_G\right). \tag{34}$$

The subscript G on A and B indicates the differential with which they are associated in applying the chain rule; e.g.,

$$(G_F\otimes A_G)\cdot\left(\frac{\partial F}{\partial r}\otimes\frac{\partial G}{\partial r}\right) = \left(G\cdot\frac{\partial F}{\partial r}\right)\otimes\left(A\cdot\frac{\partial G}{\partial r}\right).$$

The derivative of the second term in parentheses in eq. (34) with respect to F is zero, since B, H, and G are independent of F. The first term in parentheses is derived by analogy with eqs. (30)–(32) and the fact that $\partial(F\cdot G)/\partial F = G$. We obtain

$$\frac{\partial^2\varphi}{\partial F\cdot\partial G} = \frac{G_F\otimes A_G}{|G|A^2} - \frac{F\cdot G}{|G|A^4}\times(A\otimes G\wedge A + G\wedge A\otimes A). \tag{35}$$

Applying eq. (2) to replace A in the $G\wedge A$ terms and then eq. (14) to $G\wedge(F\wedge G)$, we find

$$\frac{\partial^2\varphi}{\partial F\cdot\partial G} = \frac{1}{|G|A^4}\{(A^2 + (F\cdot G)^2)\cdot G_F\otimes A_G + (F\cdot G)^2 A_F\otimes G - (F\cdot G)G^2(A\otimes F + F\otimes A)\}. \tag{36}$$

With the relation

$$(A^2 + (F \cdot G)^2) = ((F \wedge G)^2 + (F \cdot G)^2) = F^2G^2, \quad (37)$$

the factorization of G^2 and $(F \cdot G)$, and using eq. (14) for $F \wedge (G \wedge F)$, we obtain

$$\frac{\partial^2\varphi}{\partial F \cdot \partial G} = \frac{1}{|G|A^4}(G^2(A \wedge F)_F \otimes A_G + (F \cdot G)A_F \otimes (A \wedge G)_G); \quad (38)$$

and, by symmetry,

$$\frac{\partial^2\varphi}{\partial G \cdot \partial H} = \frac{-1}{|G|B^4}(G^2(B \wedge H)_H \otimes B_G + (H \cdot G)B_H \otimes (B \wedge G)_G). \quad (39)$$

We have

$$\frac{\partial^2\varphi}{\partial F \cdot \partial H} = 0. \quad (40)$$

The last term that needs to be calculated is $\partial^2\varphi/\partial G^2$. We start from eq. (25) and find

$$\frac{\partial^2\varphi}{\partial G^2} = \frac{\partial}{\partial G}\left(\frac{F \cdot G}{|G|}\right) \otimes \frac{A}{A^2} + \frac{F \cdot G}{|G|}\frac{\partial}{\partial G}\left(\frac{A}{A^2}\right) - \frac{\partial}{\partial G}\left(\frac{H \cdot G}{|G|}\right) \otimes \frac{B}{B^2} - \frac{H \cdot G}{|G|}\frac{\partial}{\partial G}\left(\frac{B}{B^2}\right). \quad (41)$$

We designate the terms on the right-hand side of eq. (41) as (41a), (41b), (41c), and (41d), respectively. The terms (41b) and (41d) can be derived by analogy with eqs. (30)–(32) and thus are symmetric. For (41a) we have

$$(41a) = \frac{\partial}{\partial G}\left(\frac{F \cdot G}{|G|}\right) \otimes \frac{A}{A^2} = \frac{1}{|G|^3A^2}(G^2F - (F \cdot G)G) \otimes A, \quad (42)$$

which can be combined with eq. (41c) and simplified using eq. (14) to give

$$(41a) + (41c) = \frac{1}{|G|^3A^2B^2}(B^2G \wedge A \otimes A - A^2G \wedge B \otimes B). \quad (43)$$

Equation (43) is compact but appears not to be symmetric. To show that it is symmetric, we apply eq. (31) twice and obtain

$$\frac{\partial^2\varphi}{\partial G^2} = \frac{1}{2|G|^3A^2}(G \wedge A \otimes A + A \otimes G \wedge A) + \frac{F \cdot G}{|G|A^4}(A \otimes F \wedge A + F \wedge A \otimes A) - \frac{1}{2|G|^3B^2}(G \wedge B \otimes B + B \otimes G \wedge B) - \frac{H \cdot G}{|G|B^4}(B \otimes H \wedge B + H \wedge B \otimes B). \quad (44)$$

ENERGY DERIVATIVES WITH RESPECT TO φ

To complete the calculation of $\partial E/\partial r$ and $\partial^2 E/dr^2$, we need the energy derivatives with respect to φ, which depend on the choice of empirical energy function. We use the expression in the CHARMM program[7]; most other programs use corresponding expressions.

For the dihedral angle, the energy expression is

$$E = K \cdot (1 + \cos(n\varphi - \varphi_0)), \quad (45)$$

or a linear combination of such terms. The derivatives are

$$\frac{\partial E}{\partial \varphi} = -K \cdot n \cdot \sin(n\varphi - \varphi_0) \quad (46)$$

and

$$\frac{\partial^2 E}{\partial \varphi^2} = -K \cdot n^2 \cdot \cos(n\varphi - \varphi_0). \quad (47)$$

The function $\cos\varphi$ is calculated from eq. (3) and $\sin\varphi$ from a simplification of eq. (4). By antisymmetric permutations in eq. (4), we have

$$\sin\varphi = \frac{G \wedge B \cdot A}{|G||A||B|}. \quad (48)$$

Using eq. (2) for B, eq. (14) for $(G \wedge (H \wedge G))$, and the fact that $G \cdot A = 0$, we find

$$\sin\varphi = \frac{|G|}{|A||B|} \cdot A \cdot H. \quad (49)$$

For a scalar computer architecture, $\cos(n\varphi)$ and $\sin(n\varphi)$ are calculated from the double recurrence relationships

$$\cos((n+1)\varphi) = \cos\varphi \cdot \cos(n\varphi) - \sin\varphi \cdot \sin(n\varphi), \quad (50c)$$

$$\sin((n+1)\varphi) = \cos\varphi \cdot \sin(n\varphi) + \sin\varphi \cdot \cos(n\varphi). \quad (50s)$$

For a vector or parallel computer architecture, we use the Tschebychev polynomials $P_n(\cos\varphi)$, ($n = 1$ to 6), to avoid loops in the vector code

$$\cos(n\varphi) = P_n(\cos\varphi), \tag{51c}$$

$$\sin(n\varphi) = \frac{1}{n}P_n'(\cos\varphi)\cdot\sin\varphi. \tag{51s}$$

Finally, the functions $\cos(n\varphi - \varphi_0)$ and $\sin(n\varphi - \varphi_0)$ are calculated by the standard trigonometric formulae

$$\cos(n\varphi - \varphi_0) = \cos\varphi_0\cdot\cos(n\varphi) + \sin\varphi_0\cdot\sin(n\varphi), \tag{52c}$$

$$\sin(n\varphi - \varphi_0) = \cos\varphi_0\cdot\sin(n\varphi) - \sin\varphi_0\cdot\cos(n\varphi). \tag{52s}$$

For the improper torsion angle, the energy is

$$E = K\cdot(\varphi - \varphi_0)^2. \tag{53}$$

The derivatives are

$$\frac{\partial E}{\partial\varphi} = 2\cdot K\cdot(\varphi - \varphi_0) \tag{54}$$

and

$$\frac{\partial^2 E}{\partial\varphi^2} = 2\cdot K. \tag{55}$$

The functions $\cos(\varphi - \varphi_0)$ and $\sin(\varphi - \varphi_0)$ are calculated with eqs. (52). Then, $(\varphi - \varphi_0)$ is calculated according to the following scheme:

1. If $\cos(\varphi - \varphi_0) > 0.1$, calculate $\arcsin(\sin(\varphi - \varphi_0))$. Otherwise:
2. Calculate $\arccos(\cos(\varphi - \varphi_0))$ and give the sign of $\sin(\varphi - \varphi_0)$. A warning is issued in this case. The warning calls attention to the fact that the angle is far from its equilibrium position so there is a large amount of energy in this term.

The value of the angle given by the inverse trigonometric function is then used in eq. (54). This scheme was chosen to improve the precision of the calculation and limit the number of tests done in the most common situations. The Fortran function ASIN was used instead of ATAN2, which would not require any test, because the evaluation of the former is significantly faster on most machines. For example, on a Convex 220, the times are ASIN → 47.3 s and ATAN2 → 107.4 s for 10,000,000 evaluations; on an HP 9000/735 the times are ASIN → 1.23 s and ATAN2 → 1.35 s for the same number of evaluations. The limit 0.1 for the cosine was chosen to minimize the frequency of switching to the arccos function, which requires an additional sign determination and the call to input/output routine because of the warning, while still keeping a reasonable precision. Since $\Delta\arcsin(x) = \Delta x/\cos\varphi$ for $\varphi = \arcsin(x)$, the loss of precision of arcsin over arccos is about one digit at the limit $\arccos(0.1) \approx 84.26°$.

For both functional forms, numerical values of $\cos\varphi_0$ and $\sin\varphi_0$ are needed. These values are calculated once from φ_0 when parameters are provided and then kept in data structures parallel to those where the force constant, periodicity etc. are stored. These data structures are built and maintained for dihedral angles, improper angles, dihedral constraints (CDIH), internal coordinate constraints, and their copies for the free energy modules (BLOCk, PERT, and TSM modules in the CHARMM program).

IRREDUCIBILITY OF $\sin\varphi = 0$ SINGULARITY IN HIGHER DIMENSIONS

It has been suggested that performing molecular dynamics in a space of higher dimensions than 3 could present advantages in conformational searching (see ref. 10 for example). In contrast to the 3-dimensional analysis given here, the $\sin\varphi = 0$ singularity for the derivative $\partial\varphi/\partial r$ has a geometrical basis in higher dimensional spaces. The singularity now is similar to the singularity of the derivative of the angle (θ) at $\sin\theta = 0$ in 3 dimensions. The direction of the derivative can be in any direction in the plane orthogonal to the line containing the three atoms, so that it is undefined. In the same way, the derivative $\partial\varphi/\partial r$ at $\sin\varphi = 0$ in a space of dimension $n > 3$ can have any direction in the subspace orthogonal to the (2-D) plane of the four atoms. This subspace has a dimension $n - 2 > 1$.

In higher dimensional spaces ($n > 3$), the derivatives $\partial\cos\varphi/\partial r$ can be obtained with standard algebra if A and B are defined[10] by $A = F - (F\cdot G)/G^2\cdot G$, $B = H - (H\cdot G)/G^2\cdot G$ and $\cos\varphi = (A\cdot B)/|A||B|$. These definitions have to be used since eq. (2) is not valid for dimensions other than 3. Thus, in the higher dimensional space, dihedral energy terms must be extremal on the surface $\sin\varphi = 0$. Also they must be an even function of φ since the sign of $\sin\varphi$ is not defined. To overcome this problem when nonplanar dihedrals

have to be maintained [e.g., pyramidal carbons as in eq. (53)], a convention has been proposed in ref. 10 where the 3-dimensional energy term is used in the projection of the coordinates onto the first three Cartesian coordinates.

Test Calculations

ACCURACY

Tests were performed with a version of CHARMM containing the new formulae. The tests were made on several machines to check whether the results depended on the machine architecture. The example studied were the ones provided with the CHARMM program as test cases. There were 93 test cases that cover the functionalities of the program; two test cases were added to test the new formulae. The results were compared with those obtained with the previous version of CHARMM that calculates the energy derivatives using cos φ. In general, the numerical differences between the two versions of CHARMM were not significantly larger than those for runs performed with the same program on different machines. For example, in a dynamics run, the output is nearly identical for about 1000 time steps and then the results begin to diverge.

An anticipated exception to the agreement between the old and new version occurred in cases where nonplanar equilibrium torsion constraints were applied. There, the old formulae have a singularity whereas the new ones do not and can thus provide the correct values, as described above. A specific example that was investigated in detail consists of a constraint of the form $V = K \cdot (\varphi - \varphi_0)^2$ applied to the dihedral angle defined by the four extended carbon of a butane molecule; the values $K = 10$ kcal/mol and $\varphi_0 = 100°$ were used. The errors of the calculated first derivatives were determined by comparing them with finite difference results. The relative error, E_R, is given by the quantity $E_R = [(F_A - F_{FD})^2/F_{FD}^2]^{1/2}$, where F_A is the 12-coordinate force vector, $-\partial E/\partial r$, calculated with the analytical formulae, and F_{FD} is the force vector calculated by finite differences. The optimal step displacement to calculate F_{FD} was found to be 10^{-5} Å; a step of 10^{-4} Å yields E_R around 10^{-8} and a step of 10^{-6} Å did not improve the result over a step of 10^{-5} (E_R about 10^{-10}), but yielded a larger noise due to the decrease of precision in the finite difference calculations. The calculated values of E_R were about 10^{-10} with the new formulae. The 10^{-10} limit is apparently due to the approximation in the calculation of F_{FD}, and thus the actual error in F_A is even smaller. Figure 2 shows the logarithm of the error as a function of the logarithm of the angle φ (in degrees). The log · log plot magnifies the errors around $\varphi = 0$; for most angles, the errors are minute. The errors of the new formulae are in the 10^{-10} range for all angles except those in the vicinity of $\varphi_0(\log_{10}(\varphi_0) = 2)$ where the forces became equal to zero and E_R is undetermined (see Fig. 2). The switching between arcsin and arccos in the new formulae occurs around 15° [i.e., $\varphi_0 - \arccos(0.1) = 100 - 84.26$; $\log_{10}(\varphi) = 1.2$]. This can be seen in Figure 2 to lead to a decrease in precision by a factor of about 3. The old formulae give a value of E_R of 10^0 around $\varphi = 0$. This is due to the fact that the old derivatives have a limiting value of zero when $\varphi \to 0$. There is a corresponding peak at 180° ($\log_{10}(\varphi) \approx 2.25$). The old formulae only reached their full accuracy around 10°, but the new formulae are always accurate. Situations where inaccuracies were introduced by the old formulae are not frequent in real systems, since an improper torsion has to be forced into a planar conformation despite a nonplanar equilibrium angle. For a dynamics simulation, this leads to a small drift in the energy and a slight bias in the generated ensemble; for a minimization, in most cases, this leads toward the correct minimum but through a different path. In the rare cases where the conformation of minimum energy corresponds to a situation where inaccura-

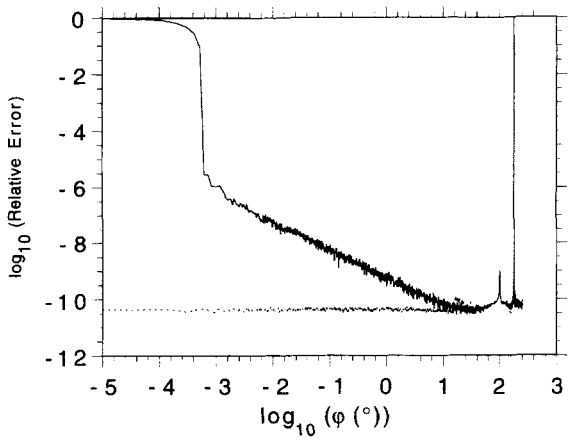

FIGURE 2. Relative errors for the first derivatives of the potential $V = K \cdot (\varphi - \varphi_0)^2$ ($K = 10$ kcal / mol, $\varphi_0 = 100°$) as a function of φ. Finite difference derivatives were used as the reference (see text). Decimal logarithm scales are used. (—) $\partial E / \partial \cos\varphi \cdot \partial \cos\varphi / \partial r$; (---) $\partial E / \partial\varphi \cdot \partial\varphi / \partial r$.

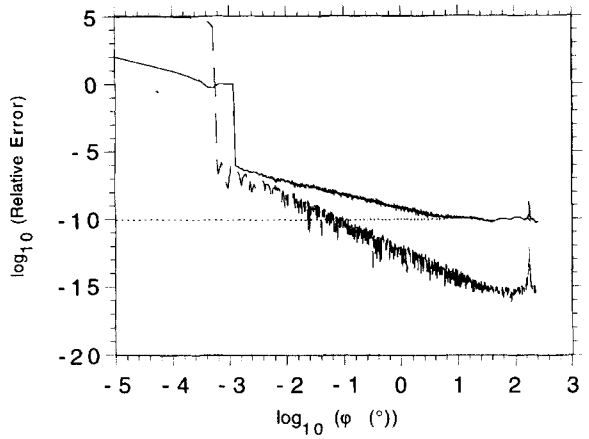

FIGURE 3. Relative errors for the second derivatives of the potential $V = K \cdot (\varphi - \varphi_0)^2$ ($K = 10$ kcal / mol, $\varphi_0 = 100°$) as a function of φ. Decimal logarithm scales are used. (—) Derivatives by cos φ and (---) derivatives by φ; finite difference derivatives of the forces were used as the reference. (– –) The derivatives by cos φ with the derivatives by φ used as reference.

cies are introduced, the minimum obtained will be slightly wrong.

For the second derivatives, the finite difference calculations are performed with respect to the forces with the same step size (10^{-5} Å). The relative errors are calculated with a formula analogous to the one used for the first derivatives where the forces are replaced by the second derivative matrix; the dot products involved consist of a sum of 144 terms. For the new formulae, we find errors on the order of 10^{-10}. As for the first derivatives, this value is probably due to the limit in the precision of the finite difference calculations (see Fig. 3 and below). The error in the second derivatives is less noisy than that of the first derivatives due to the larger number of independent terms involved (Figs. 2, 3); there are 78 independent contributions for the second derivatives versus 12 for the first derivatives. By contrast, the old formulae have an error of 10^2 for $\varphi = 0°$, in accord with the fact that the calculated derivatives are wrong. Their relative errors reached the 10^{-10} plateau around 10° ($\log_{10}(\varphi) = 1$; Fig. 3). However, the errors calculated this way could not be correct for the old formulae because the first derivatives used in the finite difference calculation of the second derivatives are wrong at small φ. Since the new formulae are correct, we used them as the reference to test the old second derivatives. Thus a relative error expression based on the new second derivative formulae instead of the finite difference was introduced (see Fig. 3). This time we found errors of at least 10^5 around $\varphi = 0$. The comparison of the two analytical second derivatives gives relative differences as low as 10^{-15} in the favorable angle range. This suggests that, in fact, the new formulae are accurate to better than 10^{-15} in all cases, confirming that the finite difference results are limited in precision. The relative error of the old formulae is in the 10^{-15} range for angles between 10° and 90° from the planar conformations.

The degree of agreement between the two second derivatives for most of the angles $\sim 10^{-15}$ is highly satisfactory and confirms, retrospectively, the equivalence of the two methods for most angles. The large errors of the old formulae at very small angles when equilibrium positions are not planar is a possible source of instabilities for minimizers using second derivatives. This is also a potentially serious problem for normal mode determination, although its space of occurrence is narrow because the local minimum in energy would have to lie within 10^{-3} degrees of $\varphi = 0$ or 180°. To experience this situation an improper term with a nonplanar equilibrium would have to be forced close to the planar conformation. This is rather unlikely but nothing would prevent it, in principle, if special parameters or constraints are used. In a large molecule the conformation of a particular improper torsion angle could be forced into a planar conformation by steric interactions. These results suggest that it would be useful to introduce the new formulae into all molecular mechanics programs, even if large errors rarely result from the use of the old formulae.

CALCULATION SPEED

Tests were performed on a Convex 220, which allowed the use of various options in the CHARMM program: slow, scalar, vector, and parallel_vector energy routines. These energy routines vary in terms of their generality of use of the code on different machines and their optimization of machine performance. Since the results are machine/compiler dependent, the following figures are only indicative of the expected performances. This is especially true for the vector code where we observed in one case that the replacement of 11 multiplications by 5 others in the course of the calculation [use of formula (49) instead of (4)] resulted in a slight slowing down of the routine. The angle derivative portion of the routine is sim-

TABLE I.
Timing for Difference Energy Routines in Seconds of CPU.

Routine	New Formulae		Old Formulae		New / Old Time
	Total CPU	Net CPU	Total CPU	Net CPU	
None	14.67	0.000	15.10	0.000	/
Slow	57.89	43.22	60.00	44.90	0.963
Scalar	50.86	36.18	53.23	38.13	0.949
Vector	43.31	28.39	41.33	26.23	1.082
Par_vect	41.31	26.64	41.57	26.47	1.006

plified by the use of the new formulae, but the energy derivative portion takes longer because it allows nonplanar equilibrium conformations. The new formulae has terms multiplied by $\sin \varphi_0$ in addition to the terms multiplied by $\cos \varphi_0$, whereas the old formulae only required $\cos \varphi_0$ terms.

We measured the speed of the routines by timing runs with a loop containing either a call to one of the energy routines or nothing. This was done by evaluating the energies and the forces 100 times for the λ repressor–operator complex,[12] which has 2296 atoms, 6351 dihedral angles, and 356 improper dihedral angles. The calculation was done with the standard parameters and the results are given in Table I. There is a slight speedup for the "setup" of the calculation in the new version of the program (see Table I, None row and Total CPU columns). This is due to the way the tables used for torsion angle calculations are filled. To increase the precision and reduce the time spent on the calculation of $\cos \varphi_0, \sin \varphi_0$, and conversion of φ_0 into radians, these variables were not calculated but assigned respectively to $(1, 0, 0)$ when $\varphi_0 = 0°$ and to $(-1, 0, \pi)$ when $\varphi_0 = 180°$. The speed of the various routines for calculating the derivatives was very similar with the old and the new formulation (see Table I). The scalar routines (slow and scalar) were slightly faster with the new formulae. This was not true for the vector and parallel vector routines where a detailed, machine oriented analysis would be needed. However, no great increase in speed is expected.

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